GUEST EDITORIAL

The Science of Cancer Health Disparities

A Young Discipline with an Old Heritage

Kevin Gardner^{*†}

From the Genetics Branch, Center for Cancer Research, National Cancer Institute, Bethesda; and the National Institute on Minority Health and Health Disparities,[†] Bethesda, Maryland*

In 1985, Margaret Heckler, the then former Secretary of Health and Human Services (1983 to 1985), released a landmark report on the health status of minorities in the United States.¹ This report revealed that, although the overall health of the general US population was improving, men and women of African ancestry and other racial and ethnic minorities showed significantly worse disease prevalence, morbidity, and mortality. The sobering conclusion from this report was that, despite the great wealth of the United States, its disadvantaged and underserved populations continued to experience an unequal burden of disease. Sadly, more than 30 years later, these health disparities continue to persist in racial and ethnic minorities, those with a low socioeconomic status, and rural populations.

The report by Heckler¹ propelled the field of health disparities onto the national stage. Although the discipline has evolved, it remains a rather young field of study. Health disparities arise from a complex interaction between societal, social, behavioral, biological, and environmental factors, including differential access to the health care system. Understanding the expansive scope and interdependent nature of the research questions associated with these factors presents a major challenge in health disparities research. As a result, the field has been characterized in multiple different ways, often from conflicting perspectives. For some, health disparities research is a population-based behavioral-social science, in which the major focus is understanding the impact of societal constructs and policies on health outcome. Reforming differences in access to care, quality of care, education, and disease prevention is the major goal of intervention. Other approaches are focused on understanding the mechanisms and pathophysiology of disease and how they are influenced by the behavioral, social, and physical environment.

Health disparities research is best described as a trans-disciplinary field of study that recognizes and studies all elements of the physical, behavioral, and social environment as important determinants of health. Thus, a major goal of health disparities research is to define and understand how these determinants interact with each other to better inform the design of more effective interventions that will ultimately reduce or eliminate the health disparity. These concepts are not new. The famed 19th-century pathologist, Rudolph Virchow (1821 to 1902), was also an early proponent of the basic concepts of epidemiology in studying disease. This is well demonstrated in his celebrated essay on poverty as the underlying cause of the 1848 typhus epidemic in Upper Silesia, then a poor rural area under Prussian control.² Virchow referred to medicine as a social science and physicians as the natural attorneys of the poor.³ Although lacking in dimension, it was one of the earliest writings to emphasize the close interaction between society, environment, and disease.

My perspective on the field of health disparities has its roots in my childhood experiences. I was born in Plainfield,

Accepted for publication August 8, 2017.

Supported by the Intramural Research Programs of the NIH, National Cancer Institute research grant ZIA-BC010847 (K.G.), Center for Cancer Research, and National Institute on Minority Health and Health Disparities research grant ZIA-MD000005 (K.G.).

Disclosures: None declared.

K.G. is Special Editor of the Race in Cancer Health Disparities Theme Issue.

Current address of K.G., Columbia University Medical Center, New York, NY.

Address correspondence to Kevin Gardner, M.D., Ph.D., Department of Pathology and Cell Biology, Columbia University Medical Center, 460 W 168th St, Room 14, New York, NY 10032. E-mail: klg2160@cumc.columbia.edu.

NJ, a small city of approximately 50,000 individuals. My father was an internist. His office was on the first floor of our house, where he saw patients. One of my most vivid memories, while growing up with my brothers and sister in the 1960s, was of my father still making house calls. I found this remarkable because there were no other physicians in the area that deemed it necessary to continue this time-honored practice of personalized medical care. One day, I asked him why. His response was simple and, although spoken with a characteristic equanimity I had grown to expect from my father, the words rang through with a subtle, yet deep, profoundness that I still carry with me to this day. He said, “you gotta know where and how people live.” As a medical student, I was reminded of this sentiment once again in the immortalized quotes of Sir William Osler, when he referred to “the good physician” as one “who treats the disease” and “the great physician” as one “who treated the patient with the disease.”^{4,pp.93} Health disparities research seeks to define and understand all aspects of the individual and the individual’s interaction with the biological, behavioral, social, and physical environment. Its goal is to elucidate and classify these differential interactions and reveal causal relationships and susceptibilities that will guide future interventions to treat and prevent diseases. Our increasing capacity to record, collect, and collate data representative of the total human experience, including survey interviews, focus groups, and mobile devices, in combination with conventional physical, physiological, and molecular measurements, has propelled us into a new data-driven scientific age. Newer emphasis will have to be placed on developing expanded capacities to examine, interrogate, and stratify how disease risk and outcome are influenced by behavioral, social, and environmental exposures, to have a greater impact on effective intervention. The emerging discipline of molecular pathological epidemiology⁵ will have a major role in addressing this need as we strive to achieve a better understanding of the ways in which where and how we live affects our overall health outcomes. In this special editorial issue for *The American Journal of Pathology* on cancer health disparities, many of these topics and concepts are presented and reviewed.

Triple-Negative Breast Cancer and African Ancestry

Triple-negative breast cancer (TNBC) is a subtype of breast cancer in which the tumor cells show low or absent expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. TNBC is highly aggressive and associated with poor prognosis. Jiagge et al⁶ review epidemiological research that compares socioeconomic status and tumor biology and describe the increased risk for TNBC in women of African descent. They review the genetics and biology of TNBC and discuss how it contributes to the overall disparities in breast cancer outcome. The authors then discuss evidence for a linkage between breast cancer stem cell and

TNBC and the use of biomarkers for their detection. Finally, they conclude by discussing recent studies in support of a hypothesis that links aspects of breast cancer stem cell biology with African ancestry.

Obesity and TNBC

Dietze et al⁷ discuss the association between metabolic health and TNBC. Herein, the authors present a brief review of the obesity epidemic and its linkage to health disparities, including food deserts, food insecurity, sedentary behavior, and lack of exercise associated with unsafe neighborhoods. They provide a discussion of the racial differences in adipose tissue distribution and critique the different anthropometric measures of obesity and their relative correlation with other measures of metabolic health. These differences are then presented in the context of the association between obesity, metabolic imbalance, and the biology of TNBC. Studies indicating that therapeutic intervention for metabolic disease may decrease risk and improve outcome for breast cancer are discussed. The article concludes with a review of the possible biological mechanisms and pathways through which obesity may promote TNBC incidence and outcome.

Colorectal Cancer Disparities

Augustus and Ellis provide an incisive review of recent studies on racial health disparities in colorectal cancer incidence and outcome.⁸ The authors discuss the role of genetic risk factors and current knowledge by comparing mendelian genetics with measures of nonmendelian genetic variation described in genome-wide association studies and their overall contribution to understanding disease risk. In addition to a critical review of the evidence for the vitamin D pathway in colorectal cancer, the authors provide a detailed assessment of current studies on the role of diet and analysis of the gut microbiome in the etiology of colon cancer disparities. This review also includes a critical overview of studies of genetic alteration, epigenetic changes, and differences in gene regulatory signatures, linked to earlier colorectal cancer onset and worse outcome. A discussion on what will be needed in future studies to advance the field is presented.

Cancer Health Disparities and Tumor Biology

Smith et al⁹ provide a concise and thought-provoking overview of mechanism-based approaches to understanding how diet, lifestyle, pathogens, and ancestral factors combine to influence racial differences in prostate and breast cancer incidence and outcomes. The authors review epidemiological data that reveal dramatic racial differences in breast and prostate cancer outcome and provide numerous examples where understanding the differences in tumor biology provides important insights. The role played by

stratifying these diseases by molecular subtype and identifying discriminating gene expression signatures, pathways, and epigenetic modification is reviewed. Finally, the authors provide an overview of the specific contribution of genomic studies, including genome-wide association studies and admixture mapping, to understanding and advancing cancer health disparities.

Race, Tissue Repair, and Cancer Health Disparities

This special issue series concludes with a conceptual perspective in which Byun et al.¹⁰ explore how genetically programed differences in tissue repair and wound healing pathways could have evolved to contribute to altered susceptibility to diseases and conditions as diverse as keloid scarring, end-stage renal disease, and invasive cancer.

Perspectives

I hope the readers of *The American Journal of Pathology* will find these review articles informative and will be motivated to include more components of health disparities research in their future studies. Health disparities research continues to be a broad and expanding discipline that will demand integrated perspectives, from clinicians, basic scientists, social scientists, pathologists, and epidemiologists, to fully address how behavioral, social, and environmental exposures contribute to disease risk and outcome. A common focus of these reviews is the impact of race on disease. Thus, it is imperative that both the reader and future health disparities researchers have an informed perspective on the challenges of applying the concepts of race and ancestry in biomedical research. The conceptualization of race has its origins in a complex history. Therefore, how and why we use the term in science remains controversial. The concept of ancestry stratifies on geographic grounds and recapitulates the grouping between populations of different ancestry.¹¹ However, ancestry need not necessarily be considered a proxy for race, because race has evolved as a social construct. Its definition is defined by history, and its meaning is shaped by social structures. Therefore, when considering race as a determinant of health disparities, one must consider the full weight and implication of its associated determinants, including socioeconomic status, social class, racism, discrimination, personal or family wealth, environmental exposures, insurance status, education, health beliefs and practices, language spoken, religion, age, diet and nutrition, and country of birth.^{12,13} These are the determinants that define where and how we live.

The precision medicine agenda is to individualize patient disease, diagnosis, and treatment, and to expand our

repertoire in the areas of predictive biology to improve disease prevention. The ability to co-stratify disease, disease risk, and exposure through profiling at the molecular, sociobehavioral, and environmental level is a central goal of the emerging field of molecular pathological epidemiology.⁵ When applied across the life course, the principles and tenets of molecular pathological epidemiology will have significant future impact on health disparities research. The challenge to achieving these goals lies in developing and refining the multidisciplinary approaches necessary to take full advantage of the growing palette of information provided by big data initiatives that seek to collect and integrate elements from the genome, proteome, metabolome, microbiome, epigenome, and exposome. Critical to this effort will be a strong commitment to representative inclusion of subjects, patients, and participants from the diverse communities and populations that comprise the United States and its territories.

References

1. Heckler M: Report of the Secretary's Task Force on Black and Minority Health. Washington, DC: US Department of Health and Human Services Task Force on Black and Minority Health, 1985
2. Brown TM, Fee E: Rudolf Carl Virchow: medical scientist, social reformer, role model. *Am J Public Health* 2006, 96:2104–2105
3. Virchow R, Rother LJ: *Collected Essays on Public Health and Epidemiology*. Canton, MA: Science History Publications, USA, 1985
4. Sir William Osler Aphorisms. Edited by Bean WB. New York: Henry Schuman Inc., 1950, pp. 93
5. Ogino S, Lochhead P, Chan AT, Nishihara R, Cho E, Wolpin BM, Meyerhardt JA, Meissner A, Schernhammer ES, Fuchs ES, Giovannucci E: Molecular pathological epidemiology of epigenetics: emerging integrative science to analyze environment, host, and disease. *Mod Pathol* 2013, 26:465–484
6. Jiagge E, Chitale D, Newman LA: Triple-negative breast cancer, stem cells, and African ancestry. *Am J Pathol* 2018, 188:271–279
7. Dietze EC, Chavez TA, Seewaldt VL: Obesity and triple-negative breast cancer: disparities, controversies, and biology. *Am J Pathol* 2018, 188:280–290
8. Augustus GJ, Ellis NA: Colorectal cancer disparity in African Americans: risk factors and carcinogenic mechanisms. *Am J Pathol* 2018, 188:291–303
9. Smith CJ, Minas TZ, Ambs S: Analysis of tumor biology to advance cancer health disparity research. *Am J Pathol* 2018, 188:304–316
10. Byun JS, Park S, Caban A, Jones A, Gardner K: Linking race, cancer outcomes and tissue repair. *Am J Pathol* 2018, 188:317–328
11. Bamshad MJ, Wooding S, Watkins WS, Ostler CT, Batzer MA, Jorde LB: Human population genetic structure and inference of group membership. *Am J Hum Genet* 2003, 72:578–589
12. Race, Ethnicity, and Genetics Working Group: The use of racial, ethnic, and ancestral categories in human genetics research. *Am J Hum Genet* 2005, 77:519–532
13. Caulfield T, Fullerton SM, Ali-Khan SE, Arbour L, Burchard EG, Cooper RS, Hardy BJ, Harry S, Hyde-Lay R, Kahn J, Kittles R, Koenig BA, Lee SS, Malinowski M, Ravitsky V, Sankar P, Scherer PW, Séguin B, Shickle D, Suarez-Kurtz G, Daar AS: Race and ancestry in biomedical research: exploring the challenges. *Genome Med* 2009, 1:8